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Children with tetralogy of Fallot exhibit accelerated maturation of the cardiac tissue into adult phenotype

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Introduction Shortly after birth, under changes in loading conditions of the heart, a shift from predominantly hyperplastic to hypertrophic cardiac growth occurs. In rodents, at birth, neonatal proliferative cardiomyocytes (CMs) exhibit a fusiform shape and differentiated into non-proliferative rod-shape CM around P20 defined as the mature state. In human, CM differentiation supposedly ended around 6 years old but the exact timing still remains unknown. Moreover, numerous stimuli most probably contribute to the CM maturation, including pressure. In a human model of pressure overload named tetralogy of Fallot (ToF), we thus hypothesized the occurrence of an earlier maturation of the cardiac tissue.

Methods we prospectively included 15 children around 6 month-old (min. 3.5 max. 27), who required surgery for the management of ToF. We assessed criteria of maturation from right ventricle tissue of infundibulum that was resected during the surgery.

Results As previously described, heart sections analysis revealed a marked sub-endocardial fibrosis ($473 \pm 444 \mu\text{m}$) and a significant fibrosis of the interstitium ($13.0 \pm 6.3\%$). This criteria was correlated to the severity of the disease represented by the degree of desaturation ($r=0.623$; $p=0.017$). In all children analysed, CMs were hypertrophied but unlike healthy myocardium, CM size was heterogeneous ($CV=40.4\%$), with alternating immature and mature area. In mature area, as expected, CMs proliferation stopped as indicated by the loss of Ki67 staining and exhibit a mature rod-shape. Ultrastructurally, CMs had structured intercalated disk and elongated contractile apparatus with an alignment of Z-strikes and apparent I-band. The lateral membrane between two CMs was compacted with periodic crests and holes.

Conclusion Our data highly suggest that the increase of pressure during childhood may act as a maturation factor. Myocardium in ToF is characterized by a shortening of the hyperplasia stage and a subsequent early hypertrophy stage.

The author hereby declares no conflict of interest

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Mechanisms of ventricular dysfunction and dyssynchrony in repaired tetralogy of Fallot: an animal study

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Background Tetralogy of Fallot (TOF) is associated with increasingly recognized late morbidity due to arrhythmias and right heart failure. Better understanding of the underlying mechanisms of these issues is needed to facilitate new therapeutic approaches. We aim to identify mechanisms generating arrhythmias in a swine model of repaired TOF with progressive right ventricular (RV) dysfunction.

Methods Surgery to mimic repaired TOF was done in 24 piglets (using a previously validated model); 24 animals served as control. Two, 4 and 6 months after surgery respectively, animals were sacrificed for subsequent analysis. Haemodynamic parameters and ventricular remodeling were analyzed by cardiac magnetic resonance (CMR) and echocardiography before sacrifice. In isolated perfused hearts, electrical activity was measured by optical mapping. Sarcoplasmic reticular calcium handling and proteins involved in calcium management were studied in single myocytes.

Results Compared with control animals, a right bundle branch block was present and the action potential (AP) duration was increased in the RV with a mechanical delay observed at 2 and 4 months post-operative in operated groups ($p<0.05$). Discordant AP alternans occurred in isolated failing hearts and calcium transient alternans in failing myocytes. These results were correlated with fibrosis revealed by CMR. Six months post-operative data are in progress.

Conclusions Electromechanical and calcium management dysfunctions are progressive in the RV and may partly explain arrhythmias in repaired TOF. These mechanisms are potential therapeutic targets for the correction of arrhythmias in failing right ventricles.

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Is high temporal resolution achievable for pediatric cardiac acquisitions during several heart beats? Illustration with cardiac phase contrast cine-MRI

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Background During pediatric cardiac Cine-MRI, data acquired during cycles of different lengths must be combined. Feinstein's model is used to project multiple cardiac cycles of variable lengths into a mean cycle.

Methods 1/The temporal errors during Feinstein's projection were computed in 306 cardiac cycles fully characterized by tissue Doppler imaging with 6-phase analysis (from a population of 7 children and young adults). 2/The effects of these temporal errors on tissue velocities were assessed by simulating a typical tissue phase mapping acquisition and reconstruction. 3/Myocardial velocities curves, extracted from high-resolution phase-contrast cine images, were compared for the 6 volunteers with lowest and highest heart rate variability, within a population of 36 young adults.

Results 1/The mean of temporal misalignments was 30ms over the cardiac cycle but reached 60ms during early diastole. 2/During phase contrast MRI simulation, early diastole velocity peaks were diminished by 5cm/s leading to virtual disappearance of isovolumic relaxation peaks. 3/The smoothing and erasing of isovolumic relaxation peaks was confirmed on tissue phase mapping velocity curves, between subjects with low and high heart rate variability ($p=0.05$).

Conclusions Feinstein cardiac model creates temporal misalignments that impair high temporal resolution (notably for phase contrast cine imaging) in a population of high heart rate variations such as in paediatrics (figure next page).

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Neonatal arterial switch operation: the sooner the better!

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Objective To evaluate the impact of preoperative management on in-hospital post-operative outcomes after an arterial switch operation (ASO) in newborns with transposition of the great arteries (TGA)

Methods In this retrospective monocentric study, we included all newborns with TGA±ventricular septal defect who underwent an ASO between 2008 and 2014. Collected data included demographics, clinical and anatomic characteristics, and preoperative management (Rashkind, prostaglandin infusion, mechanical ventilation, age at surgery). Univariate and multivariate analyses were performed to study the impact of preoperative characteristics on time to extubation, a surrogate marker of postoperative morbidity.